PATENT COOPERATION TREATY

CONFIRMATION

From the INTERNATIONAL SEARCHING AUTHORITY

To:

Ella Cheong
Spruson & Ferguson
PO Box 1531
Robinson Road Post Office
Singapore 903031

RECEIVED
23 AUG 2004
KJR
BY:

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

	Date of mailing *(day/month/year)* 18 AUG 2004
Applicant's or agent's file reference 9869sg136kjr	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No. **PCT/SG2004/000166**	International filing date *(day/month/year* 4 June 2004
Applicant GENOME INSTITUTE OF SINGAPORE et al	

1. [X] The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.
Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):
When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.
Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35
For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:
[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

Reminders

Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/AU	Authorized officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	**DAVID OLDE** Telephone No. (02) 6283 2569

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule" and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasised that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, eg. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Preliminary Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

(i) the claim is unchanged;
(ii) the claim is cancelled;
(iii) the claim is new;
(iv) the claim replaces one or more claims as filed;
(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement, under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

If a demand for international preliminary examination is made, the written opinion of the International Searching Authority will, except in certain cases where the International Preliminary Examining Authority did not act as International Searching Authority and where it has notified the International Bureau under Rule 66.1*bis*(b), be considered to be a written opinion of the International Preliminary Examining Authority. If a demand is made, the applicant may submit to the International Preliminary Examining Authority a reply to the written opinion together, where appropriate, with amendments before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later (Rule 43*bis*.1(c)).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide*, Volume II.

PATENT COOPERATION TREATY

From the:
INTERNATIONAL SEARCHING AUTHORITY

To:

Ella Cheong
Spruson & Ferguson
PO Box 1531
Robinson Road Post Office
Singapore 903031

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	18 AUG 2004
Applicant's or agent's file reference 9869sg136kjr	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SG2004/000166	4 June 2004	4 June 2003

International Patent Classification (IPC) or both national classification and IPC
Int. Cl.[7] C12Q 1/68 C12N 15/11 C12N 15/12 G06F 19/00

Applicant
GENOME INSTITUTE OF SINGAPORE et al

1. This opinion contains indications relating to the following items:

- [X] Box No. I — Basis of the opinion
- [ ] Box No. II — Priority
- [ ] Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [X] Box No. IV — Lack of unity of invention
- [X] Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI — Certain documents cited
- [ ] Box No. VII — Certain defects in the international application
- [X] Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the IPEA/AU
AUSTRALIAN PATENT OFFICE
PO BOX 200, WODEN ACT 2606, AUSTRALIA
E-mail address: pct@ipaustralia.gov.au
Facsimile No. (02) 6285 3929

Authorized Officer
DAVID OLDE
Telephone No. (02) 6283 2569

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SG2004/000166

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing
      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ in written format
      ☐ in computer readable form

   c. time of filing/furnishing

      ☐ contained in the international application as filed.
      ☐ filed together with the international application in computer readable form.
      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SG2004/000166

Box No. IV Lack of unity of invention

1. ☐ In response to the invitation (Form PCT/ISA/206) to pay additional fees the applicant has:

   ☐ paid additional fees

   ☐ paid additional fees under protest

   ☐ not paid additional fees

2. ☒ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

The international application does not relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. The requirement of unity of invention under Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" relates to those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

This application is directed to the identification of marker genes indicative of hepatocellular carcinoma (HCC) that can be used to determine the presence or absence of HCC cells or tissues. However this concept is not new. See for example:

a) Graveel, C.R. *et al.* 2001. Expression profiling and identification of novel genes in hepatocellular carcinomas. Oncogene. 20:2704-2712.

b) Tackels-Horne, D. *et* al. 2001. Identification of differentially expressed genes in hepatocellular carcinoma and metastatic liver tumors by oligonucleotide expression profiling. Cancer. 92(2):395-405.

Okabe, H. *et al.* 2001. Genome-wide analysis of gene expression in human hepatocellular carcinomas using cDNA microarray: Identification of genes involved in viral carcinogenesis and tumor progression. Cancer Research. 61:2129-2137.

Each of these citations disclose the identification of 2 or more markers that are indicative of HCC.

Thus while a common feature of the applicant's markers may be that they are present in HCC tissue and not normal liver tissue, this is not considered a special technical feature as markers with such properties are well known in the art (see above documents).

(Continued on supplemental sheet)

4. Consequently, this opinion has been established in respect of the following parts of the international application:

   ☒ all parts

   ☐ the parts relating to claims Nos.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/SG2004/000166

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims 1-54	YES
	Claims -	NO
Inventive step (IS)	Claims -	YES
	Claims 1-54	NO
Industrial applicability (IA)	Claims 1-52	YES
	Claims 53, 54	NO

Citations and explanations:

The invention appears to reside in the identification of four (4) sets of markers, disclosed as Tables 1-4, that appear to be specific for hepatocellular carcinoma (HCC) (See for example Table 5). From the specification it appears that DNA chips containing each set of markers may be used in diagnosis, therapy and monitoring progression or regression of hepatocellular carcinoma with high predictive accuracy.

NOVELTY(N) AND INVENTIVE STEP(IS)

The following citations identified in the order presented in the ISR have been referred to for the purposes of this report:

D1: Smith. 2003. Cancer Research.

This citation discloses microarray screening of 13600 genes expressed in HCC v non-tumorous tissue of which 674 were differentially expressed with 273 being up-regulated in HCC tissue. From this analysis a set of 50 markers was obtained and presented as a fingerprint for HCC diagnosis and prognosis.

D2: Li. 2003. Biochips.

This citation discloses microarray analysis of differentially expressed genes in HCC compared to normal tissue. 4096 genes were screened with 109 over-expressed and 794 under-expressed in HCC tissue compared to normal tissue. There use in diagnostics is also disclussed.

D3: Chen. 2002. Molecular Biology of the Cell.

This citation discloses microarray screening of 23,000 clones with 1,640 genes differentially expressed in HCC v normal tissue. There use in distinguishing HCC from other tumors based on global gene expression is also discussed.

D4: Li. 2002. Journal of Cancer Research and Clinical Oncology.

This citation discloses the microarray screening of 12,800 genes associated with HCC. 1,820 were found to have an altered expression pattern in HCC v normal tissue. Discusses the use of up- and down-regulated genes for fingerprinting and diagnosing HCC.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/SG2004/000166

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claims 1-54 are not clear in regard to the phrase "consist essentially". It is not clear whether the phrase refers to the complete set of markers in each table or a subset of markers in each table. Hence the claims are not clear in regard to this phrase.

Claims 1-54 are not clear in respect of the phrase "fragments, variants or analogues". From the specification the invention resides in the use of specific markers to identify HCC. It is not clear how fragments, variants or analogues of the identified sequences retain specificity to enable the promise of the invention.

Claim 5 is not clear as the dependent claim number is missing.

The scope of claims 1-54 are not fully supported by the description. These claims are directed to the compositions or methods containing at least 2 nucleic acids. In contrast, from a reading of the specification as whole, the invention is seen to reside in the use of the set of markers identified by each of Tables 1-4 in the screening of HCC (See for example Table 5). There does not appear to be support for the selection and use of any 2 or more markers from any of Tables 1-4 to identify HCC. Thus as the claims are not limited to the use of the complete set of markers disclosed in each of Tables 1, 2, 3 or 4 in compositions or methods of screening for HCC, the scope of the claims extends beyond that of the specification. Hence the claims are not fully supported by the description.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International Application No.

PCT/SG2004/000166

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: **Box IV (Unity)**

Thus there does not appear to be a special technical feature common to all markers identified in the specification. Thus it would appear that the special technical features of the specification relate to the use of the sets of markers identified in each of Tables 1-4. ie the use of all the markers in either Table 1, 2, 3 or 4 for the identification of HCC with high predictive accuracy. Further there does not appear to be a special technical feature common to all four sets of markers as they contain different numbers of markers, hence the application is directed to four (4) inventions as follows:

1) The markers identified in Table 1 when used to determine the presence or absence of HCC cells or tissues.

2) The markers identified in Table 2 when used to determine the presence or absence of HCC cells or tissues.

3) The markers identified in Table 3 when used to determine the presence or absence of HCC cells or tissues.

The markers identified in Table 4 when used to determine the presence or absence of HCC cells or tissues.

The ISA has chosen not to ask for additional fees as all four inventions can be covered by the one search statement relating to the identification and use of molecular markers able to determine the presence or absence of HCC.

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: **Box V (Novelty and Inventive Step)**

D5: Okabe. 2001. Cancer Research.

This citation discloses microarray screening of 23,040 genes resulting in 165 up-regulated and 170 down-regulated in HCC v normal tissue. The use of these markers in screening for HCC and in producing diagnostics is also discussed.

D6: Graveel. 2001. Oncogene.

This citation discloses expression profiling and identification of genes involved in HCC using oligonucleotide microarrays as well as the identification of rare transcripts using representational difference analysis (RDA) (p2706-707, Table 2). Identifies genes that were significantly differentially expressed in tumors as compared to normal quiescent state. Discloses that such genes may serve as markers for the altered proliferation characteristics of HCC.(p2705 Col 2), Also that 162, 297 and 69 genes had altered expression between various tumor states and normal tissue (p.2705 col 1, Table 1).

D7: Tackels-Horne. 2001. Cancer.

This citation discloses gene analysis between primary HCC and metastatic hepatic neoplasm with normal liver tissue. They used Affymetric Gene Chip technology to screen over 6,000 full length human gene sequences and the Human 35K set of arrays (chips A-D) representing over 35,000 additional genes or ESTs. Identified 842 genes and ESTs over-expressed in HCC and 393 genes/ESTs under-expressed in HCC compared with normal liver tissue (Tables 3, 4, 5) as well as 243 genes uniquely expressed in HCC and not in normal liver tissue. Also discloses the use of these sequences as markers to monitor disease states, disease progression, drug screening and drug efficacy on either multigene platforms or single gene assays.

D8: Xu. 2001. Proceedings of the National Academy of Sciences (USA).

This citation discloses the use of microarrays from various sources to screen for differentially expressed genes in HCC normal tissue. Findings included 884 genes up-regulated and 1369 genes down-regulated.

(Continued on supplemental sheet)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: **Box V (Novelty and Inventive Step)**

Claims 1-54 lack an inventive step in light of the D1.

These claims are directed to compositions comprising addressable collections of HCC markers which are differentially expressed in HCC v normal tissue and the use of such markers in diagnostic and screening methods related to HCC.

The problem to be solved is to identify molecular markers of hepatocellular carcinoma (HCC). Applicant solves this problem using microarray analysis of expressed genes in HCC v normal liver tissue.

D1 discloses a similar procedure with the identification of differentially expressed genes using microarray technology (See above). As such applicant's invention is seen as nothing more than a technical equivalent of the methods of D1. Thus no inventive merit can be acknowledged for claims directed to 2 or more markers differentially expressed in HCC v normal tissue. Further, D1 discloses a set of 50 markers that can be used to fingerprint HCC tumours. This is seen to be analogous to applicant's marker sets in Tables 1-4. Thus there is not seen to be any inventive merit in claiming a set of markers specific for HCC in light of the disclosure of D1. The use of a set of markers for diagnosing HCC and screening compounds to treat HCC are also discussed in D1 and are considered by the examiner to be obvious goals once HCC tissue can be successfully identified. Thus there is not seen to be any inventive merit in claims directed to the use of markers or marker sets in these endeavours.

Therefore in the absence of surprising properties attributable to the applicant's sets of markers and limitation of the claims to the complete sets of markers as disclosed in any one of Tables 1-4, the claimed invention lacks an inventive step.

Similar objections are raised against claims 1-54 in respect of each of the citations D2-D8. Therefore in the light of each of D2-D8, the claimed invention lacks an inventive step.

INDUSTRIAL APPLICABILITY(IA)

Claims 1-52 meet the requirements of the PCT in terms of Industrial Applicability.

Claims 53 and 54 are not industrially applicable. These claims refer to a database comprising information. As such the claim is directed to the mere presentation of information and as such is not industrially applicable.

PATENT COOPERATION TREATY

PCT

COPY

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
9869sg136kjr		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/SG2004/000166	4 June 2004	4 June 2003

Applicant

GENOME INSTITUTE OF SINGAPORE et al

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (See Box No. II).

3. ☒ **Unity of invention is lacking** (See Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the drawings to be published with the abstract is Figure No. 1

☒ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2004/000166

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

The international application does not relate to one invention only or to a group of inventions so linked as to form a single general inventive concept. The requirement of unity of invention under Rule 13.1 shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" relates to those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.

This application is directed to the identification of marker genes indicative of hepatocellular carcinoma (HCC) that can be used to determine the presence or absence of HCC cells or tissues. However this concept is not new. See for example:

Graveel, C.R. *et al*. 2001. Expression profiling and identification of novel genes in hepatocellular carcinomas. Oncogene. 20:2704-2712.

(Continued on supplemental sheet)

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SG2004/000166

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C12Q 1/68 C12N 15/11 C12N 15/12 G06F 19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
SEE ELECTRONIC DATABASES

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
SEE ELECTRONIC DATABASES

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CaPlus, WPIDS (hepatocellular carcinoma, array or chip, differential, profile, gene expression, gene profile, microarray, DNA chip, gene chip, hepatocellular carcinogenesis), Medline (gene expression profiling/CT, oligonucleotide array sequence analysis/CT, protein array analysis/CT, carcinoma, hepatocellular/CT)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

ıtegory*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Smith, M.W. *et al.* 2003. Identification of novel tumor markers in hepatitis C virus-associated hepatocellular carcinoma. Cancer Research. 63:859-864. See whole document.	1-54
X	Li, Y. *et al.* 2003. DNA microarray analysis of gene expression profiles in hepatocellular carcinoma. Biochips. pp51-59. See whole document.	1-54
X	Chen, X. *et al.* 2002. Gene expression patterns in human liver cancers. Molecular Biology of the Cell. 13:1929-1939. See whole document. Note: This citation refers to supplemental information, including clone lists, provided on the authors' web site: http://genome-www.stanford.edu/hcc/supplement.shtml	1-54

[X] Further documents are listed in the continuation of Box C [ ] See patent family annex

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 August 2004	18 AUG 2004
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer **DAVID OLDE** Telephone No : (02) 6283 2569

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Li, Y. *et al.* 2002. Discovery and analysis of hepatocellular carcinoma genes using cDNA microarrays. Journal of Cancer Research and Clinical Oncology. 128:369-379. See whole document.	1-54
X	Okabe, H. *et al.* 2001. Genome-wide analysis of gene expression in human hepatocellular carcinomas using cDNA microarray: Identification of genes involved in viral carcinogenesis and tumor progression. Cancer Research. 61:2129-2137. See whole document.	1-54
X	Graveel, C.R. *et al.* 2001. Expression profiling and identification of novel genes in hepatocellular carcinomas. Oncogene. 20:2704-2712. See whole document.	1-54
X	Tackels-Horne, D. *et* al. 2001. Identification of differentially expressed genes in hepatocellular carcinoma and metastatic liver tumors by oligonucleotide expression profiling. Cancer. 92(2):395-405. See whole document.	1-54
X	Xu, X-R, *et* al. 2001. Insight into hepatocellular carcinogenesis at transcriptome level by comparing gene expression profiles of hepatocellular carcinoma with profiles of hepatocellular carcinoma with those of corresponding nincancerous liver. Proceedings of the National Academy of Sciences (USA). 98(26):15089-15094. See whole document. Note: this citation refers to Tables 4-6 and Figure 3 displayed as supplemental information with the electronic copy of the citation on the PNAS website: http://www.pnas.org/cgi/content/full/98/26/15089/DC1	1-54

Supplemental Box
(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: III (Unity)

b) Tackels-Horne, D. *et* al. 2001. Identification of differentially expressed genes in hepatocellular carcinoma and metastatic liver tumors by oligonucleotide expression profiling. Cancer. 92(2):395-405.

c) Okabe, H. *et al.* 2001. Genome-wide analysis of gene expression in human hepatocellular carcinomas using cDNA microarray: Identification of genes involved in viral carcinogenesis and tumor progression. Cancer Research. 61:2129-2137.

Each of these citations disclose the identification of 2 or more markers that are indicative of HCC.

Thus while a common feature of the applicant's markers may be that they are present in HCC tissue and not normal liver tissue, this is not considered a special technical feature as markers with such properties are well known in the art (see above documents).

Thus there does not appear to be a special technical feature common to all markers identified in the specification. Thus it would appear that the special technical features of the specification relate to the use of the sets of markers identified each of Tables 1-4. ie the use of all the markers in either Table 1, 2, 3 or 4 for the identification of HCC with high predictive accuracy. Further there does not appear to be a special technical feature common to all four sets of markers as they contain different numbers of markers, hence the application is directed to four (4) inventions as follows:

1) The markers identified in Table 1 when used to determine the presence or absence of HCC cells or tissues.

2) The markers identified in Table 2 when used to determine the presence or absence of HCC cells or tissues.

3) The markers identified in Table 3 when used to determine the presence or absence of HCC cells or tissues.

4) The markers identified in Table 4 when used to determine the presence or absence of HCC cells or tissues.

The ISA has chosen not to ask for additional fees as all four inventions can be covered by the one search statement relating to the identification and use of molecular markers able to determine the presence or absence of HCC.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

RECEIVED PCT
16 JUL 2004
KJR
BY:

To:

Ella Cheong Spruson & Ferguson
PO Box 1531
Robinson Road Post Office
Singapore 903031

NOTIFICATION OF RECEIPT OF SEARCH COPY

(PCT Rule 25.1)

Date of mailing *(day/month/year)*	24 JUN 2004 (24/6/2004)
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
9869sg136kjr	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/SG2004/000166	4 JUN 2004 (4/6/2004)	4 JUN 2003 (4/6/2003)

Applicant

Genome Institute of Singapore (et al.)

1. **Where the International Searching Authority and the receiving Office are not the same Office:**

The applicant is hereby notified that the search copy of the international application was received by this International Searching Authority on the date indicated below.

Where the International Searching Authority and the receiving Office are the same Office:

The applicant is hereby notified that the search copy of the international application was received on the date indicated below.

24 JUN 2004 (24/6/2004) *(date of receipt).*

2. ☐ The search copy was accompanied by a nucleotide and/or amino acid sequence listing in computer readable form.

3. **Time limit for establishment of international search report**

The applicant is informed that the time limit for establishing the international search report is three months from the date of receipt indicated above or nine months from the priority date, whichever time limit expires later. The Australian Patent Office, as proposed as part of the Customer Service Charter is committed to establishing the international search report within 9 weeks of receiving the international search fee.

4. A copy of this notification has been sent to the International Bureau and, where the first sentence of paragraph 1 applies, to the receiving Office.

Name and mailing address of the ISA/AU **AUSTRALIAN PATENT OFFICE** **PO BOX 200, WODEN ACT 2606, AUSTRALIA** E-mail: pct@ipaustralia.gov.au Facsimile No. 02 6285 3929	Authorized officer MRS KATRINA SEIVERS 02 62832815 Telephone No.

Form PCT/ISA/202 (July 1998)